Neural stem cell-mediated CE/CPT-11 enzyme/prodrug therapy in transgenic mouse model of intracerebellar medulloblastoma.

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Public Summary:
Medulloblastoma is a heterogeneous diffuse neoplasm that can be highly disseminated, and is the most common malignant childhood brain tumor. Although multimodal treatments have improved survival rates for patients with medulloblastoma, these tumors are associated with high morbidity and mortality. New treatment strategies are urgently needed to improve cure rates and, importantly, to spare normal brain tissue from neurotoxicity and patients from life-long cognitive and functional deficits associated with current therapies. In numerous preclinical brain tumor models, neural stem cells (NSCs) have shown great promise as delivery vehicles for therapeutic genes. Here, we have used an established, genetically modified human NSC line (HB1.F3.CD) to deliver carboxylesterase (CE) to cerebellar tumor foci and locally activate the prodrug camptothecin-11 (CPT-11; Irinotecan) to the potent topoisomerase I inhibitor SN-38. HB1.F3.CD NSC tumor tropism, intratumoral distribution and therapeutic efficacy were investigated in clinically relevant experimental models. Magnetic resonance imaging was used for in vivo tracking of iron nanoparticle-labeled NSCs, and to assess the therapeutic efficacy of CE-expressing HB1.F3.CD cells. As compared with controls, a significant decrease in tumor growth rate was seen in mice that received both NSCs and CPT-11 as their treatment regimen. Thus, this study provides proof-of-concept for NSC-mediated CE/CPT-11 treatment of medulloblastoma, and serves as a foundation for further studies toward potential clinical application.Gene Therapy advance online publication, 8 March 2012; doi:10.1038/gt.2012.12.

Scientific Abstract:
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